(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 November 2001 (29.11.2001)

PCT

(10) International Publication Number
WO 01/89679 A2

(51) International Patent Classification[7]: B01J 2/20, 2/22, A61K 9/16, A61J 3/00

(21) International Application Number: PCT/US01/15597

(22) International Filing Date: 14 May 2001 (14.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/576,373 22 May 2000 (22.05.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CONTINUOUS PRODUCTION OF PHARMACEUTICAL GRANULATION

(57) Abstract: A single pass, continuous, automated system for producing a pharmaceutical granulation includes multiple feeders to feed powders and liquids, a twin screw processor to granulate, a radio frequency or microwave based drying apparatus to dry the granulation, and at least one mill to process the dried granulation to desired particle sizes. The system incorporates means for monitoring key process parameters on-line. The granulation produced can be compressed into a tablet or incorporated into a capsule, both having a uniform distribution of the active ingredient. The system produces product having consistent properties even when production is scaled up for manufacture of the tablet in commercial volume. A single pass, continuous, automated system for producing a high dose pharmaceutical granulation from a low density active ingredient, includes multiple feeders to feed powders and liquids, a twin screw processor to granulate, a radio frequency or microwave based drying apparatus to dry the granulation, and at least one mill to process the dried granulation to desired particle sizes. The system produces product having consistent properties even when production is scaled up for manufacture of the tablet in commercial volume. The twin screw processor has first and second conveying elements, with a mixing element in between the conveying elements, and the second conveying element has at least one pitch less than at least one pitch of the first conveying element. The system also permits the optimization of a number of other design parameters, such as a location and feed rate of a side stuffer and a liquid feeder, the rotational speed of the granulator itself, and the final granulation size. The system is particularly suitable for producing a granulation of nelfinavir mesylate along with excipients, including calcium silicate, for a high dose product.

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CONTINUOUS PRODUCTION OF PHARMACEUTICAL GRANULATION

FIELD OF THE INVENTION

The present invention relates to a method and apparatus for producing a pharmaceutical granulation product which is typically compressed into tablets or filled into hard gelatin capsules. More particularly, it pertains to a single-pass automated system and an apparatus for continuous production of a pharmaceutical granulation which incorporates wet granulation, drying, and milling.

The present invention also relates to a method for producing a high dose (greater than 200 mg strength active ingredient) pharmaceutical granulation product which can be compressed into tablets or filled into hard gelatin capsules.

BACKGROUND OF THE INVENTION

Granulation is a critical unit operation in the manufacture of solid oral dosage forms. Even with constant improvements in tableting equipment for automating production and increasing product output, powder granulation must still possess specific physical properties to ensure smooth operation in downstream processing. Thus, consistent product quality is often the most important motivation that guides advances in granulation techniques. Other significant goals are maintaining regulatory compliance, reducing cycle times, increasing process efficiency, and achieving production cost savings.

Advancements in wet granulation technology include high shear mixer granulators, single pot processing with a high shear mixer granulator and microwave drying, and a high shear granulator integrated with a fluid bed dryer, such as a semi-continuous multi cell apparatus. While these techniques provide some advantages over previously used granulation methods, there are specific shortcomings with each technique and, most importantly, none provide a true continuous granulation process starting with individual ingredients or a powder blend.

For example, in a single pot microwave based granulator using a high shear mixer, blending and agglomeration are accomplished by an impeller, while a chopper imparts high mechanical agitation to the blend of ingredients. Even though this granulator allows short processing time and the option of drying within the same equipment, the granulator is not efficient in granulating cohesive materials; it produces non-uniform shaped and sized granules; it degrades fragile granules; it allows uncontrolled granule growth; and it produces granules with low porosity.

In addition, Glatt GmbH (of Binzen Germany) has disclosed the use of a semi-continuous system (the "Glatt Multicell GMC") in which small batches of raw materials are conveyed in successive batches into a high shear, mixer-granulator which mixes and granulates the materials. The wet granulation is sequentially vacuum conveyed through a series of three fluid bed dryers for drying. Each unit operation occurs sequentially as the mini-batch moves through the system.

In contrast to high shear and fluid bed granulation processes, discussed above, the present invention can be easily scaled-up. Since the process is continuous, the batches of various sizes can be manufactured using the same piece of equipment. Therefore, the scaling up of the process from one size batch to a larger size batch is predictable.

Granulating of high dose and/or low bulk density actives using the traditional high shear mixers and fluid bed granulators is extremely difficult and at times impossible. The materials tend to ride on the sides of the bowl mixers during the granulation process, requiring intermittent manual scraping. Even then, there is no assurance that the distribution of the active within the granulation is uniform. More particularly, in the case of low density active ingredients, such as nelfinavir mesylate, increases in drug loading in the granulation process lead to wet granulations with an undesirable "taffy-like" consistency. Additionally, attempts to use high shear wet granulation on blends of nelfinavir mesylate and calcium silicate at a ratio of 3:1, respectively, resulted in tablets having enhanced dissolution and disintegration but which were not bioequivalent to the marketed product. Fluid bed granulation of such a formulation is also less than ideal. As a

does not ensure "coating" of the active by the excipients. The situation is particularly critical when very cohesive materials are processed. These drawbacks have been overcome by using the current invention, a twin screw granulator.

For drying ingredients during the manufacture of pharmaceutical products, conduction and convection have been the two most prevalent heating methods used. For drying pharmaceutical solids, use of convection is preferred to use of conduction because conductive heat transfer requires temperatures that would potentially result in product degradation. Nevertheless, in convective drying, either a high volume of air flow or long residence times are required to achieve the required reduction in moisture levels. In some instances, vacuum conditions are used to further enhance the removal of the evaporated moisture. The high volume of air flow or long residence times from convective drying can degrade or otherwise damage a pharmaceutical product produced therefrom. To a lesser degree, microwave energy has also been used, but only in batch mode. At present, no conventional drying systems provide a true single pass drying process with a first in-first out principle.

Therefore, there exists a need for a granulation process, a drying process, and a single pass, fully automated, continuous system which enables production of pharmaceutical granulation with consistent physical properties.

There also exists a need for a granulation process, a drying process, and a single pass, fully automated, continuous system which enables production of a high dose pharmaceutical granulation of a low density active ingredient with consistent physical properties.

SUMMARY OF THE INVENTION

The present invention provides a single pass continuous, automated process for producing a granulation product, which can be further processed to make a solid oral dosage form, such as a tablet or capsule.

In one embodiment, the present invention comprises a twin screw wet granulator-chopper (TSWGC), to which active ingredient(s) and solid and liquid

additives are fed, which mixes, granulates, and wet mills those components to form a granulation product.

In another embodiment, the present invention comprises a drying apparatus which dries granulation using dielectric energy, such as radio frequency energy, low frequency (conventional) microwave energy, or high frequency (millimeter wave) microwave energy, in a continuous, single pass mode, optionally incorporating a product isolation tunnel.

In a further embodiment, the present invention comprises integrated, automated process control of the components of the system such that key process parameters and product properties are monitored along the length of the system; for example, the moisture content of the granulation and the uniformity of the distribution of active ingredient(s) are monitored on-line.

Another aspect of the present invention is a continuous processing system for producing a high dose pharmaceutical granulation. The system comprises the twin screw wet granulator-chopper, a powder feeder adapted to feed a powder to the twin screw wet granulator-chopper, and a liquid feeder adapted to feed a liquid to the twin screw wet granulator-chopper. Both the powder feeder and the liquid feeder are coupled to the twin screw wet granulator-chopper and adapted to feed the powder and the liquid at an inlet of the twin screw wet granulator-chopper.

The twin screw wet granulator-chopper comprises first and second conveying elements, each having at least one conveying element pitch, as well as a first mixing element positioned in between conveying elements. Additionally, the twin screw wet granulator-chopper comprises at least one chopping element positioned to contact the pharmaceutically active ingredient after conveying elements. With regard to the conveying elements, at least one pitch of the second conveying element is less than at least one pitch of the first conveying element.

Another aspect of the invention is a process for producing a high dose pharmaceutical granulation comprising feeding a powder comprising a pharmaceutically active ingredient to a twin screw wet granulator-chopper and contacting a liquid and the powder with a first conveying element of a twin screw wet granulator-chopper. The liquid and powder are then contacted with a first mixing element to form a wet mass, which is contacted with the second conveying

contacted with a chopping element of the twin screw wet granulator-chopper and chopped into a granulation.

The present invention provides a single pass continuous, automated process for producing a high dose (greater than 200 mg strength) granulation product of a low density active ingredient, which can be further processed to make a solid oral dosage form, such as a tablet or capsule.

In yet another embodiment, the present invention comprises a twin screw wet granulator-chopper, to which active ingredient(s) and solid and liquid additives are fed, which mixes, granulates, and wet mills those components to form a high dose granulation product.

It is to be understood that both the foregoing general description and the following detailed description are exemplary, but are not restrictive, of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is best understood from the following detailed description when read in connection with the accompanying drawing. It is emphasized that, according to common practice, the various features of the drawing are not to scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

Figure 1 is a schematic block diagram of the process and apparatus according to the present invention;

Figure 2 is schematic representation of a twin screw wet granulator-chopper according to the present invention;

Figure 3A is one embodiment of the twin screw granulator-chopper according to the present invention;

Figure 3B is another embodiment of the twin screw granulator-chopper according to the present invention;

Figure 4 is an isometric view of the feeder system of the twin screw granulator-chopper according to the present invention;

Figure 5 is a schematic representation of the drying apparatus according to the present invention; and

Figure 6 is a schematic representation of an electrode configuration useful in the drying apparatus according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises an automated, single pass system, including process and apparatus, for continuous production of pharmaceutical granulation that can be further processed to make solid oral dosage forms. This system includes a twin screw wet granulator-chopper (TSWGC); a single pass drying apparatus which uses dielectric energy, such as radio frequency (RF), microwave energy, or both. These components produce a granulation having superior properties when incorporated into a pharmaceutical product. The TSWGC may be used in combination with the dielectric energy-based drying apparatus or, alternatively, it may be used separately with conventionally used components, such as a fluid bed or a continuous paddle dryer. In addition, the dielectric energy-based drying apparatus may be used with the TSWGC or, alternatively, it may be used separately with conventionally used components, such as a high shear granulator.

The TSWGC overcomes the limitations of conventional wet granulation equipment. The TSWGC comprises conveying, mixing, granulating and chopping elements to achieve distributive and, when desired, dispersive mixing. The design and alignment of the screw elements can be varied to process active ingredients and additives of varying bulk densities so that a homogeneous granulation product is produced. The TSWGC provides product densification and uniformity that exceeds the capabilities of a high shear granulator and, when used with the dielectric-based drying apparatus of the present invention, has drying speeds equivalent to or better than that of a fluid bed granulator/dryer.

The TSWGC differs from conventional extruders in several ways. The exit point is open-ended as opposed to a die plate in a conventional extruder; it has extended shafts that may optionally protrude out from the open end; and chopping

elements are located at the exit end. It has one or more powder and liquid feeding zones, with a custom designed feeding zone for simultaneous feeding of liquid and powder. An additional feature of TSWGC is a shaft retainer seal, which prevents the forward motion of the screw shaft during operation.

The active ingredient(s) and additives (i.e., excipients, binders, plasticizers, etc.) are fed into the TSWGC such that: (1) solid ingredients are fed using multiple loss-in-weight type feeders which continuously monitor the weight of solid ingredients being fed; and (2) liquid ingredients are fed using multiple pumps combined with mass flow meters or loss-in-weight type feed tanks. The feed barrels can be modified for simultaneous feeding of liquids and powders, at one or more locations along the length of the TSWGC.

The TSWGC mixes and granulates the active ingredient(s) and additives using a twin screw processor. The threads of the screw elements are arranged to optimize mixing and granulation to achieve the required granulate structure for the active ingredient(s) and additives being granulated. This arrangement enables wet milling within the TSWGC, which obviates the need for a separate wet milling step. The active ingredient(s) and additives are fed directly into the TSWGC. In addition, the arrangement of the conveying elements and the venting devices at the feed point remove entrapped air and maximize product throughput. The TSWGC utilizes liquids to heat and cool the granulation and to provide more uniformity in temperature and better temperature control at the temperatures used for granulation.

The wet granulation exits the twin screw processor through the open end as discrete granulation particles, optionally passing through a screen which is discussed further below. The granulation particles are then leveled and deposited uniformly onto the belt of the drying unit using a load/leveling device. The drying unit uses dielectric energy, such as RF or microwave energy, to remove moisture from the granulation in a one pass, continuous mechanism. Further, the drying unit is designed to have proper air flow for moisture removal, and the electrodes used in the drying unit are designed so that they may be offset and tilted, when required, such that moisture is removed while maintaining the granulation in the desired temperature range. Once dried, the granulation is transported to the

size of the dried granulation is reduced by an appropriate mill, such as a hammer mill, cone mill, fitz mill, pin mill, or other appropriate screening device.

The components of the system for producing the granulation product may be controlled by a master controller, which adjusts parameters in the system in response to production conditions measured at various points/components along the system. The parameters and conditions are measured on-line so that the system is continuous with each element of material produced having the same processing/shear history. For example, the moisture content of the granulation and the uniformity of the distribution of active ingredient(s) are monitored on-line, and feedback is provided to the individual components which allows the operator to make adjustments of conditions. More specifically, the moisture content of the granulation product can be measured, for example, after it exits the TSWGC or after it is dried, and if that measurement is outside of the tolerated range (e.g., 0%-10% after drying), conditions can be appropriately adjusted.

The composition of the resulting granulation is more homogeneous and uniform than conventionally produced granulation. In addition, the transfer of the present invention's technology for commercial production is quicker than if using conventional, non-continuous processes because fewer scale-up steps are involved in the system of the present invention.

As shown schematically in Figure 1, this system comprises a TSWGC having two or more screws rotating in the same or opposite directions for the granulation stage 7.4. To the TSWGC, one or more solid and/or liquid materials are fed, typically including at least one pharmaceutically active ingredient, at feed stages 7.1-7.3. The active ingredient(s) combined with excipients, water, and possibly other additives, are continuously introduced at one or more points along the length of the TSWGC. Alternatively, and preferably in the production of a high dose product, the dry ingredients are preblended in a known way, for example, in a twin shell or bin blender before being introduced to the TSWGC.

In the TSWGC 1, as shown in Figures 2, 3A, 3B, and 4, the solid ingredients are fed through one or more side or top powder feeders 2 and liquid ingredients are fed through a top or bottom feeder 4, all near the upstream end of the TSWGC 1. The liquid ingredients are injected into the TSWGC 1 by a pump 3

relatively homogeneous wet mixture as they travel along the length of the TSWGC 1.

More specifically, as shown in Figures 3A and 3B, a typical arrangement of the twin screw elements used in the TSWGC 1 of the present invention comprises a housing 9 containing conveying elements 6, mixing (granulating) elements 8, and chopping elements 10 which achieve distributive and, when desired, dispersive mixing. These elements produce a homogeneous granulation with the required densification to enhance the ease of further processing in making the desired solid oral dosage form. The TSWGC 1 of the present invention is capable of processing active ingredients and additives with varying bulk densities to produce a homogeneous granulation.

The TSWGC of the present invention is characterized based on the diameter of its screw elements. For example, a TSWGC with a screw diameter of 18 mm is referred to as an 18 mm TSWGC. The screw diameter is generally between about 16 mm and about 135 mm. The length of individual barrels (housing) 9, i.e., the length of the entire granulating zone, is designed to be a multiple of the screw diameter. Generally, the ratio of the length of the housing to the screw diameter is between about 20:1 and about 60:1. Nevertheless, this ratio may be altered to accommodate any specific requirements of the granulating process.

The length of the individual elements in the housing is generally in multiples of 15 mm. The pitch of the conveying element 6 is generally between about 15 mm and about 180 mm depending on the size of the machine and the requirements for the particular granulating process. For example, for a 50 mm screw, the pitch of the conveying elements is generally between about 20 mm and about 72 mm. The pitches of the various conveying elements used in the present invention are discussed in more detail below.

The pitch, for bilobal element, is the distance along the axis of the screw between two adjacent even- or odd-numbered flights of the conveying elements.

For mixing and chopping functions, several different designs can be used, including but not limited to kneading discs, combing mixers, gear mixers, pin mixers, and calender gap mixers, depending on the ingredients being granulated.

of reverse threads, kneading elements, and/or gear elements 8 to enhance the mixing process.

In general, wet granulation stage 7.4 in the TSWGC operates at room temperature, although the temperature may be raised, to increase the solubility of poorly soluble active ingredients, for controlled release purposes, to assist in the drying process, or for any other reason to affect product characteristics. Temperature within the TSWGC may be maintained by a heat exchange fluid, circulated in a jacket surrounding the housing 9 of the TSWGC 1, although electric heating may also be used.

In one embodiment of the invention, as shown in Figures 3A and 3B, combing choppers 8 and 10 are used for mixing and chopping in a TSWGC 1 with a 34 mm or 27 mm screw diameter having a housing length/screw diameter ratio of 28:1. In each combing mixer 8, there are five rows of vanes 19 with 8 passages within each row. The vanes 19 are protrusions from a ring-like structure with gaps in between each vane 19. The gaps between adjacent rows of vanes are alternating so that there are gaps between the rows which facilitate mixing of the granulation. In one embodiment, the vanes are at a pitch angle of 120° toward the output end of the TSWGC which allows the granulation to be pushed through the TSWGC. A flat pitch or other pitch angles can also be used depending on the ingredients being granulated.

The screw sizes, threads, pitches, and angles of contact with the housing 9 and granulation may vary depending on the active ingredient(s) and excipients being mixed into a granulation product and the extent of production. In any case, conventionally used extruder screws may be incorporated into the TSWGC.

The twin screw wet granulator-chopper screw design comprises first and second conveying element sets, each having at least one set of conveying element pitch, as well as a first mixing element positioned in between conveying elements. With regard to the conveying elements, at least one pitch of the second conveying element set is less than at least one pitch of the first conveying element. That is, the pitches of the conveying elements are progressively reduced along the length of the conveying element. This arrangement (progressive reduction) leads to simultaneous de-aeration and densification as the granulation traverses the length

of the machine. For example, a powder comprising a low density active ingredient, such as nelfinavir mesylate, may have a density of about 0.2 g/mL upon entering the TSWGC of the present invention, and exit the TSWGC as a granulation having a density of about 0.5 g/mL or more.

It is important that the pitch of each succeeding conveying element is preferably less than or equal to the pitch of the preceding conveying element. This arrangement provides gradual densification while preventing material buildup and enabling the process to have a steady output rate, as described above. A preferred method of introducing the low density active ingredient into the TSWGC is through the use of a conventional side-stuffer.

The size of the equipment will dictate the available pitches for use as is understood by one of ordinary skill in the art.

The chopping element 10 shown in Figures 3A and 3B are positioned at the terminal end 12 of the TSWGC 1 to eliminate lumps in the granulation and to maintain the structure of the granulation. Additionally, the shaft length may be extended so that the chopping element 10 at the terminal end 12 may be flush with the open end of the barrel or extend further out (as shown in Figure 3B) by an additional 1 to 60 mm, preferably about 1 to 30 mm, to further assist in maintaining the formation of discrete granules. Also, the TSWGC 1 contains an optional guard device and chute 12, Figures 3A and 3B, to assist in maintaining the path of the wet granulation for further processing and an optional discharge bin 17 for receiving discarded waste materials.

As shown in the exemplary TSWGC 1 of Figures 3A and 3B, the TSWGC 1 includes a relief vent 11; a retention seal 13 and a combination drive motor and gear reducing elements 15 for rotating the twin screws. Unlike conventional twin screw extruders, the TWSGC of the present invention does not include a die at its outlet end. Rather, housing 19 is open at the outlet end of the twin screw extruders, and granulated product exits therefrom freely.

The wet granulation process variables, such as the extruder barrel temperature profile, screw speed, screw design, and rate of adding different mix components are controlled in response to various downstream requirements (variables), such as the granulation bulk density, moisture level, uniformity of

temperature, and product material inventory at any stage following mixing, granulation, and chopping. Specifically, dried granulation moisture and the uniformity of distribution of active ingredient(s) are monitored on-line for optimal product composition. In addition, the control system may include alarm or warning signals to indicate various processing parameters or events, such as an error condition system overload or unacceptable product characteristics.

Upon exiting the TSWGC, the wet granulation is deposited and leveled (stage 7.6 in Figure 1) to the appropriate height and thickness on the drying belt by a load/leveling device. The granulation is then transported by the load/leveling device into a drying stage (7.7 in Figure 1) to undergo drying preferably induced by dielectric energy, such as RF or microwave energy. Optionally, the wet granulation may be further processed in a wet mill (stage 7.5 in Figure 1) before being conveyed to the dryer. The granulation may also be dried by other processes and apparatus, such as paddle, fluid bed, or infrared drying with or without the application of a vacuum.

The drying stage 7.7 may comprise, as illustrated in Figures 5 and 6, a RF generator 22 which creates an alternating electric field between the two electrodes 24. For RF sources, based on international ISM (Industrial, Scientific, Medical) standards, the frequencies used are 27.12 MHz and 40.56 MHz. The frequencies used for microwave dryers are 915 MHz and 2450 MHz for low frequency, and several gigahertz in case of millimeter wave, for high frequency. The material to be dried is conveyed between the electrodes. The design enables a single pass, continuous, drying system.

The dried granulation is removed from the drying belt and conveyed (stage 7.9 in Figure 1) into an on-line mill, such as a cone mill, via another device/conveying mechanism, for milling (stage 7.10 in Figure 1) the granulation into the sizes typically used in pharmaceutical dosage forms. Depending on the reactivity of the product material, this may be done under nitrogen or other inert gas atmosphere. After exiting the dry mill, the milled granulation is optionally blended with other commonly used excipients prior to being compressed into tablets or filled into hard gelatin capsules.

As shown in Figures 5 and 6, the drying apparatus 20, which uses RF

between two electrodes 24 positioned on opposite sides of the apparatus 20. The material to be dried enters the drying apparatus 20 at its input end 26 and is conveyed by a drying belt 28, powered by a drive motor 44. A load/leveler device levels the wet granulated material on the drying belt 28 at the required height. The leveler device forms a bed of granulated material that travels along the belt 28 through the drying zone at a predetermined speed. The belt 28 can be continuously cleaned by a belt cleaning mechanism 48.

As the granulation enters the portion of the drying apparatus 20 containing the electrodes 24, the material to be dried is acted upon by the alternating electric field created by the electrodes 24 which heats the material. An optional inner tunnel 46 may be inserted to further isolate the product without impeding the distribution of RF energy. Electrodes 24 along with ground electrode 25 are used to produce the electric field. The electrodes 24 are arranged in a specific manner to allow for controlled heating of the granulation bed. Different electrode configurations such as parallel plate (as shown in Figure 5), staggered rod, etc. may be used. The number of electrodes may be increased depending on the energy requirements for drying particular materials.

The friction caused by constant reorientation of water molecules under the influence of the alternating electric field between the electrodes 24 causes the water in the material to rapidly heat and evaporate. Water vapor is removed from the top and/or bottom of the surface of belt 28 by process air that flows in a co-current (same direction) or counter current (opposite direction) direction as the granulation product is conveyed on the belt. This process air flow is caused by conveying heated 34 and cooled 36 streams of conditioned air. A cooling system 38, with regulator 40, regulates the temperature of the RF generator 22 by regulating the temperature of a circulating stream 42 flowing around RF generator 22. Controller 40 may also control other parameters and other conditions to optimize drying of the granulated product. Attenuators 32 at both the input 26 and output ends 30 prevent radiation leakage from the tunnel 20.

Thus, as the material to be dried (the granulation bed) moves through the drying apparatus/tunnel, the moisture level of the material gradually decreases. The material is maintained in a relatively narrow temperature range to maximize

During drying, the bed can be maintained at a temperature range determined by the nature of the product, usually within about a 30° range, such as from about 75°C to about 105°C. Nevertheless, using RF energy, it is possible in principle to achieve the required moisture removal at temperatures as low as room temperature. If tolerated by the active ingredient(s) and excipients being granulated, temperatures above 105°C may also be used. Typical residence times in the tunnel vary from several minutes to a few hours, depending on the required inlet/outlet moisture levels, the properties of the product, and the required product output.

The amount of heat generated in the RF drying apparatus is determined by the frequency of the dielectric energy, the square of the voltage applied across the electrodes, the dimensions of the material being dried, and the dielectric loss factor of the material being dried (this represents the ease with which the material can be heated by this method). Dielectric heating is volumetric in nature. Given its polar nature, water is selectively and volumetrically heated when placed in the drying apparatus of the present invention. The selective and volumetric heating increases the rate of heat transfer compared to that of conventional heating/drying systems and reduces the residence time in the drying apparatus, which is preferable to protect materials that may degrade at elevated temperatures. The selective heating of water and in situ evaporation of moisture largely eliminates temperature and moisture variations in the dried material and, thus, can improve product quality and/or further processing of the dried material.

The use of dielectric energy, i.e., RF or microwave energy, for drying obviates the need to convey the material to be dried through the drying zone more than once for sufficient drying of the material.

The dried material is conveyed out of drying apparatus 20 by belt 28 through output end 30 of drying apparatus 20. From drying apparatus 20, the dried material is conveyed and further processed by a milling device to particle sizes suitable for compression into a tablet or incorporation into a hard gelatin capsule or sachet.

The present invention also comprises an automated, single-pass system, including a process and apparatus, for continuous production of a high dose

(greater than 200 mg strength active ingredient) pharmaceutical granulation of a low density active ingredient/excipient blend (for example, a bulk density of the blend of about 0.2 g/mL or less) that can be further processed to make solid oral dosage forms.

This system includes a twin screw wet granulator-chopper (TSWGC) adapted to granulate a low density active ingredient/excipient blend into a form suitable for processing into a high dose product. Therefore, the components produce a granulation having superior properties when incorporated into a pharmaceutical product. As described above, when tablets are produced from a granulation of the present invention, the number of tablets typically administered daily may be significantly reduced, often by about 40-60%. The system may be used in combination with the dielectric energy-based drying apparatus or, alternatively, it may be used separately with conventionally used components, such as a fluid bed or a continuous paddle dryer.

Prior to applicants' invention, no commercially feasible techniques or systems were available to produce a high strength dosage form of nelfinavir mesylate. Applicants' development of twin screw wet granulation technology for the manufacture of a high dose product is possible because the degree of mixing and shear imparted by the twin screw wet granulation chopper is much higher than the shear and mixing that is available on conventional wet granulation equipment, thereby greatly increasing density of the granulation. Therefore, a powder comprising a low density active ingredient, such as nelfinavir mesylate, may have a density of about 0.2 g/mL upon entering the TSWGC of the present invention, and exit the TSWGC as a granulation having a density of about 0.5 g/mL or more.

The TSWGC overcomes the limitations of conventional wet granulation equipment. The TSWGC comprises conveying, mixing, granulating, and chopping elements to achieve distributive and, when desired, dispersive mixing. The design and alignment of the screw elements can be varied to process active ingredients and additives of varying bulk densities so that a homogeneous granulation product is produced. The TSWGC provides product densification and uniformity that exceeds the capabilities of a high shear granulator.

For producing a granulation for a high dose product, the temperature may vary from about 25°C to about 50°C, typically about 25°C. However, with a low density active ingredient, such as nelfinavir mesylate, when the temperature is about 50°C the granules produced in the system are larger and harder. However, the overall dissolution performance of the granules was not affected by temperature variations.

The wet granulation process variables may be adjusted. It was found that by adjusting the parameters, it is possible to manufacture a high dose product of a low density active ingredient, i.e., nelfinavir mesylate, thereby reducing the overall number of tablets that must be administered daily. Prior to this discovery, no commercially feasible techniques or systems were available to produce a high strength dosage form of nelfinavir mesylate. Applicants' development of twin screw wet granulation technology for the manufacture of a high dose product is possible because the degree of mixing and shear imparted by the twin screw wet granulation chopper is much higher than the shear and mixing that is available on conventional wet granulation equipment, thereby greatly increasing active ingredient density of the granulation.

In addition to low density active ingredients such as nelfinavir mesylate, any suitable active ingredient that can be formulated into a solid dosage form can be used in the process, apparatus, and system of the present invention. However, the parameters described above are specifically for the production of a high strength granulation of a low density active ingredient, and specifically for nelfinavir mesylate. Examples of the therapeutic indications and specific active ingredients are listed below.

1. Antipyretic, analgesic, and anti-inflammatory agents, such as indomethacin, aspirin, diclofenac sodium, ketoprofen, ibuprofen, mefenamic acid, dexamethasone, hydrocortisone, prednisolone, acetaminophen, phenylbutazone, flufenamic acid, sodium salicylate, tramadol hydrochloride tablets, oxaprozin, and etodolac.
2. Antiulcer agents, such as omeprazole, cimetidine, lansoprazole, nizatidine capsules USP, ranitidine hydrochloride, famotidine, and nizatidine.

3. Coronary vasodilators, such as nifedipine, isosorbide dinitrate, diltiazem hydrochloride, dipyridamole, isosorbide monotrate, verapamil, nicardipinenifedipine, and nitroglycerin tablets.
4. Peripheral vasodilators, such as sildenafil citrate, cinepazide maleate, cyclandelate, and pentoxiphylline.
5. Antibiotics, such as ampicillin, amoxicillin, cefalexin, clarithromycin tablets, cefuroxime axetil tablets, cefropzil, erythromycin ethyl succinate, bacampicillin hydrochloride, minocycline hydro-chloride, chloramphenicol, tetracycline, and erythromycin.
6. Synthetic antimicrobial agents, such as nalidixic acid, enoxacin, cinoxacin, levofloxacin tablets, ofloxacin, norfloxacin, ciprofloxacin hydrochloride, and sulfamethoxazole-trimethoprim.
7. Antispasmodic agents, such as propantheline bromide, atropine sulfate, and scopolamine.
8. Antitussive and antiasthmatic agents, such as theophylline, aminophylline, codeine phosphate, dextromethorphan hydrobromide ephedrine hydro-chloride, and noscapine.
9. Bronchodilators, such as salbutamol sulfate, pir-buterol hydrochloride, bitolterol mesilate, clenbuterol hydrochloride, terbutaline sulfate, mabuterol hydrochloride, fenoterol hydrobromide, and methoxyphenamine hydrochloride.
10. Diuretics, such as furosemide, acetazolamide, trichlormethiazide, cyclothiazide, hydrochlorothiazide, hydroflumethiazide, spironolactone, and triamterene.
11. Muscle relaxants, such as tolperisone hydrochloride, eperisone hydrochloride, tizanidine hydrochloride, mephenesin, chlorzoxazone, phenprobamate, methocarbamolbaclofen, and dantrolene sodium.
12. Cerebral metabolism improving agents, such as meclofenoxate hydrochloride.
13. Tranquilizers, such as oxazolam, diazepam temazepam, meprobamate, nitrazepam, and chlordiazepoxide, sulpiride, clocapramine hydrochloride, zotepine, chlorpromazine, and haloperidol.

14. Beta-blockers, such as pindolol, propranolol hydrochloride, metoprolol tartrate, labetalol hydrochloride, oxprenolol hydrochloride, acebutolol hydrochloride, metoprolol succinate, bufetolol hydrochloride, alprenolol hydrochloride, and nadolol.

15. Antiarrhythmic agents, such as procainamide hydrochloride, disopyramide, quinidine sulfate, propafenone hydrochloride, and mexiletine hydrochloride.

16. Antigout agents, such as allopurinol, probenecid, colchicine, warfarin sodium tablets USP, and sulfinpyrazone.

17. Anticoagulants, such as ticlopidine hydrochloride, dicoumarol, and warfarin potassium.

18. Antiepileptics, such as gabapentin capsules, gaphenytoin, divalproex sodium, sodium valproate, and metharbital.

19. Antihistaminics, such as loratadine, cetirizine hydrochloride, chlorpheniramine maleate, fexofenade hydrochloride, clemastine fumarate, and cyproheptadine hydrochloride.

20. Antiemetics, such as difenidol hydrochloride, metoclopramide, and trimebutine maleate.

21. Antihypertensive agents, such methyldopa, prazosin hydrochloride, bunazosin hydrochloride, clonidine hydrochloride, budralazine bisporolol fumarate and hydrochlorothiazide, terazosin hydrochloride, and urapidil.

22. Sympathomimetic agents, such as dihydroergotamine mesilate, isoproterenol hydrochloride, and etilefrine hydrochloride.

23. Expectorants, such as bromhexine hydrochloride, carbocysteine, and cysteine methyl ester hydrochloride.

24. Oral antidiabetic agents, such as glibenclamide, glumepiride tablets, glipizide, metformin hydrochloride tablets, troglitazone, tolbutamide, and glymidine sodium.

25. Iron preparations, such as ferrous sulfate and dried iron sulfate.

26. Vitamins, such as vitamin B_{12}, vitamin B_6, vitamin C, and folic acid.

27. Therapeutic agents for pollakiuria, such as flavoxate hydrochloride, oxybutynin hydrochloride, and terodiline hydrochloride.

28. Angiotensin converting enzyme inhibitors, such as enalapril maleate, enalaprilat USP, fosinopril sodium tablets, alacepril, lisinopril, quinapril hydrochloride tablets, ramipril, and delapril hydrochloride.

29. Other types of active ingredients, such as acetohexamide, ajamaline, alendronate sodium, amlodipine besylate, amylobarbitone, atorvastin calcium, bendrofluozide, benzbromarone, benzonatate, benzylbenzoate, betametharzone, brand of paroxetine hydrochloride, bupropion hydrochloride, buspirone HCl USP, chloramphenicol, chlorpropamide, chlorthalidone, clofibrate, conjugated estrogens tablets USP, corticosteroids, diazepam, dicumerol, digitoxin, digoxin, dihydroxypropyltheophylline, diltiazem HCl, doxazosin mesylate, ergot alkaloids, ethotoin, felodipine, fluoxetine hydrochloride, fluconazole, fluvastatin sodium, frusemide, glutethimide, griseofulvin, hydrochlorothiazide, hydrocortisone, hydroflumethiazide, hydroquinone, hydroxyalkylxanthines, indomethacin, isoxsuprine hydrochloride, ketoprofen, khel-lin, levothyroxine sodium USP, losartan potassium tablets, lovastatin USP, meprobamate, nabilone, nelfinavir mesylate, nefazodone hydrochloride, nicotinamide, nifedipine, nitrofurantoin, novalgin, nystatin, papaverine, paracetamol, phe-nylbutazone, phenobarbitone, pravastin sodium, prednisolone, prednisone, primadonel reserpine, risperidone, romglizone, salicylic acid, salmeterol xinafoate, sertraline hydrochloride, simvastatin, spironolactone, sulphabenzamide, sulphadiamadine, sulphamethoxydiazine, sulphamerazine, succinylsulphathiazole, sulphamethizole, sulphamethoxazole, sulphathiazole, sulphisoxazole, sumatriptan succinate, testosterone, tolazoline, tolbutamide, trifluoperazine, trimethoprim, valsartan capsules, zolpidem tartrate, and other water insoluble active ingredients.

The excipients (polymers, small molecules, and organic and inorganic compounds) which may be used in the present invention can be any natural or synthetic substance that can be used as a raw material in the manufacture of pharmaceutical products. Examples of excipients include: hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate

succinate, carboxymethylethylcellulose, cellulose acetate phthalate, Eudragit acrylic copolymers, methacrylic copolymer LD, methacrylic copolymer S, aminoalkyl methacrylate copolymer E, poly(vinyl acetal) diethylaminoacetate, polyvinylpyrrolidone, ethylcellulose, methacrylic copolymer RS, polyvinyl alcohol, high molecular weight polyethylene glycols, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium, dextrin, pullulan, Aca-cia, tragacanth, sodium alginate, propylene glycol alginate, agar powder, gelatin, starch, processed starch, phospholipids (such as lecithin), glucomannan, cetanol, medium chain triglycerides, polyoxyethylene-polyoxypropylene glycol (Pluronic), macrogols (200, 300, 400, 600, 1000, 1500, 1540,4000, 6000, 20000), polyethylene glycols, such as PEG 200, PEG 300, PEG 400, and PEG 600, triacetin, and triethyl citrate (Citroflex), Tweens 20, 60, and 80, Span 20, Span 40, Pluronics, polyoxyethylene sorbitol esters, monoglycerides, polyoxyethylene acids, polyoxyethylene alcohols and mixtures thereof, calcium carbonate, dibasic calcium phosphate dihydrate, calcium sulfate, microcrystalline cellulose, lactose, magnesium carbonate, magnesium oxide, maltodextrim, mannitol, sucrose, compressible sugar, croscarmellose, crospovidone, sodium starch glycolate, pregelatinized starch, guar gum, alginic acid, ascorbic acid, citric acid, cyclodextrin, dextrates, colloidal silicon dioxide, sodium benzoate, sodium bicarbonate, and talc.

The excipients can be used independently or, if necessary, in a combination of two or more types of excipients. The processing parameters, such as pressure, temperature, feed rate of material, amounts and feed rates of water and other excipients used in the production process of the present invention are dependent on the type of active ingredient and excipients, among other conditions. Moreover, the combination of operating parameters of the system must be set such that the active ingredient and excipients will be maintained at temperatures below their decomposition points and the desired characteristics of the pharmaceutical product will be achieved.

Certain aspects of the present invention are illustrated by the examples, which follow. In the examples below, continuous wet granulation, drying, and milling were evaluated by producing a tablet containing an investigational drug

TSWGC, as shown in Figure 2. In Example 2, the granulation produced by the TSWGC was dried in a drying apparatus/tunnel using dielectric energy, specifically, radio frequency energy (as shown in Figures 5 and 6) (the granulation produced in Example 1 was dried by a conventional method). In the examples below, continuous wet granulation, drying, and milling were evaluated by producing a granulation containing nelfinavir mesylate utilizing the TSWGC of the present invention, specifically, a co-rotating TSWGC. Examples 3 and 4 illustrate the production of a high dose product from a low density active ingredient. The examples are meant by way of illustration only and do not serve to limit the scope of the present invention.

EXAMPLE 1

Production of Investigational 300-mg Tablet

A pre-blend of an investigational drug and excipients was prepared by mixing the weighed ingredients, in a 16 qt V-blender. The blend of dry ingredients was fed from a loss-in-weight solid feeder into the TSWGC configured with a side stuffer mechanism. The feeder was adjusted to yield a feed rate of 11.4 kg/hour. An aqueous solution containing a surfactant was used as a granulating fluid and injected into the TSWGC using a piston pump at a rate of 8.64 kg/hour. A total of 6.8 liters of the fluid were used for this product. The temperature of the TSWGC was maintained at 26°C, and the screw speed was 177 rpm at a maximum torque of 19%.

The granulation was prepared by the TSWGC with an output of 18.2 kg/hour. The granulation was dried in a tray dryer at 50°C for 9 hours from a moisture level of 13.6% to a moisture level of 1.0%.

The dried granulation was milled in a hammer mill, and the final blend of product was prepared by mixing the milled granulate product with the listed external excipients in a V-blender. The fillers and disintegrant were added to the milled granulation product and blended for 10 minutes at 20 rpm. Then, lubricant was added to the resulting product and blended for another 5 minutes at 20 rpm.

Tableting was performed using a six station tablet press. The final blend was compressed using standard concave oval tooling, having the dimensions

0.645" × 0.3295" × 0.0465", at a press speed of 30 rpm. A compression profile (as shown in Table 1) was generated by compressing the blend over a range of applied forces.

The results of physical testing on the investigational drug formulation, are also outlined in Table 1: (1) the formulation exhibited good compressibility and disintegration with the tablet cores disintegrating within 6 minutes; and (2) the dissolution testing results (not shown in Table 1) indicated complete release of investigational drug within 20 minutes from all individual tablets.

Table 1. Investigational Drug Tablets—Physical Testing

Compression Force (kN/kg)	Hardness (kPa) (n = 10)	Disintegration (minutes) (n = 3)	Friability (%) (n = 20) Time = 10 Minutes
5.16/526.3	9.1 ± 0.5	2.0	0.88
7.17/731.3	14.2 ± 0.8	3.0	0.35
8.07/823.1	16.3 ± 0.9	3.7	0.32
9.27/945.5	19.3 ± 1.3	4.7	0.18
11.77/1200.5	24.2 ± 1.4	5.3	0.18

EXAMPLE 2

Production of Investigational 600-mg Tablet (Higher Strength)

A pre-blend of an investigational drug, at a higher strength than in Example 1, and excipients was prepared by mixing the weighed ingredients for 20 minutes at 25 rpm in a 42 liter bin blender. The powder blend was then introduced into the TSWGC according to the present invention by a side stuffer feed mechanism (as shown in Figures 2-4). Three pairs of mixing elements in combination with different sized conveying elements were used.

The dry ingredients were fed from a loss-in-weight solid feeder configured with a side stuffer mechanism connected to a hopper containing the solid ingredients. A vertical agitator was used to mix the contents of the hopper. The feed rate of the powder feed was 10.5 kg/hour. An aqueous solution containing a surfactant was used as a granulating fluid and injected into the TSWGC using a

this product. The temperature of the TSWGC was maintained at 26°C and the screw speed was 200 rpm at a maximum torque of 35%. The granulation was prepared by the TSWGC with an output of 14.5-15.1 kg/hour. The granulation was dried in a drying tunnel using radio frequency energy from a moisture level of 22.9% to a moisture level of less than 2.0%. The granulation was laid down on a 24 inch wide belt. The granulation bed was 22 inches wide and 1 inch deep, and the belt speed was 0.26 feet/minute.

The dried granulation was milled in a hammer mill and the final blend of product was prepared by mixing the milled granulate product and external excipients in a V-blender. The fillers and disintegrant were added to the milled granulation product and blended for 10 minutes at 20 rpm. Then, lubricant was added to the resulting product and blended for another 5 minutes at 20 rpm.

Tableting was performed using a six station tablet press. The final blend was compressed using standard concave oval tooling, having the dimensions 0.7" × 0.355" × 0.07", at a press speed of 30 rpm. A compression profile was generated by compressing the blend over a range of applied forces.

The results of physical testing on the high strength investigational drug formulation are outlined in Table 2: (1) the formulation exhibited good compressibility and disintegration with the tablet cores disintegrating within seven minutes; and (2) the dissolution testing results indicate complete release of drug within 20 minutes from tablets compressed over the entire hardness range.

Table 2. High Strength Investigational Drug Tablets—Physical Testing

Compression Force (kN/kg)	Hardness (kp) (n = 10)	Disintegration (min) (n = 3)	Friability (%) (n = 20) Time = 10 Minutes
4.66/475.5	8.5 ± 0.9	4.2	2.76
6.03/614.7	12.0 ± 0.9	5.5	1.38
6.58/671.0	13.7 ± 1.1	5.3	0.82
8.54/870.8	18.9 ± 1.2	6.0	0.39
9.93/1012.5	22.3 ± 1.7	6.9	0.49

EXAMPLE 3

Production of Nelfinavir Mesylate Granulation and High-Dose Tablet

A. Pre-Blend

The pre-blending unit operation was performed in a twin-shell blender. Each portion of nelfinavir mesylate and calcium silicate was blended for 15 minutes. The density of each material was between 0.1 to 0.15 g/cc. The pre-blends were then discharged in fibre drums lined with polyethylene bags.

B. Twin-Screw Wet Granulation

The low density pre-blend was fed into the twin screw wet granulator (modified 34 mm Leistritz), via the side-stuffer unit into the second barrel. The granulator setting was 350 rpm, and the side-stuffer setting was 207 rpm. The dry pre-blend was fed at 3.0 to 3.2 kg/hour. Liquid was injected from 16 to 25 mL/ minute. Venting of displaced gas occurred in the first barrel. Liquid was injected into both the second barrel and the third barrel. The elements were arranged to decrease in pitch, thus volume capacity, as the material was further processed through the granulating system. An output of high density wet granulation from 3.9 to 4.2 kg/hour was observed. The granulation was then dried in a fluidized bed. Using the granulation obtained, a high dose tablet was prepared. Tableting is performed by utilizing equipment and techniques well-known in the art.

While this invention has been described with respect to specific embodiments thereof, it is not limited thereto. In its most general sense, this invention encompasses a twin screw granulator-chopper and/or radio frequency or microwave dryer used to produce a pharmaceutical granulation, and a single pass, continuous system for producing such products incorporating the granulator-chopper, the dryer, or both. Examples are provided that illustrate the production of a high dose product from a low density active ingredient. Nor is the present invention limited to the examples shown. Rather, various modifications may be made in the details of the invention and its various embodiments as described and exemplified without departing from the true spirit and scope of the invention. The claims which follow should be construed accordingly.

CLAIMS

What is claimed is:

1. A single pass continuous processing system for producing pharmaceutical granulation, comprising:

(a) powder and liquid feeders to provide at least one pharmaceutically active ingredient and additives;

(b) a twin screw wet granulator-chopper device for granulating the active ingredient and additives received from the powder and liquid feeders into a wet granulation product said twin screw wet granulator-chopper including a housing surrounding said device, said housing including a nonextruding opening at the outlet thereof;

(c) conveying, loading, and leveling means for conveying the wet granulation from the outlet of said twin screw wet granulator-chopper, loading the wet granulation on a dryer belt, and leveling the wet granulation to the desired height;

(d) a drying apparatus for receiving the wet granulation from the dryer belt and drying the wet granulation using dielectric energy;

(e) conveying means for transporting the dried granulation from the drying tunnel for size reduction;

(f) a mill for reducing the dried granulation to particles of a desired size; and

(g) control means for controlling process variables of at least one of the powder and liquid feeders, the twin screw wet granulator-chopper, the conveying, loading, and leveling means, the drying apparatus, the conveying means, and the mill to optimize production of pharmaceutical granulation.

2. The system of Claim 1 wherein the powder is fed through a side-stuffer unit, and the liquid is fed into a liquid injector for addition into the twin screw wet granulator-chopper.

3. The system of Claim 1 wherein the twin screw wet granulator-chopper comprises a mechanism for chopping the granulation into discrete particles.

4. The system of Claim 1 wherein the pitches of the conveying elements are reduced progressively along the length of the conveying element.

5. The system of Claim 1 wherein powder is fed into the device at the same position where at least a portion of the liquid is injected into the device.

6. The system of Claim 1 wherein the control means includes means for monitoring conditions of the system and controlling process variables of at least one of the powder and liquid feeders, the twin screw wet granulator-chopper, the conveying, loading, and leveling means, the drying apparatus, the conveying means, and the mill.

7. The system of Claim 6 wherein the moisture content of the granulation is monitored on-line and the liquid feeder is controlled to adjust the moisture content.

8. The system of Claim 6 wherein the uniformity of distribution of the active ingredient is monitored on-line and at least one of the powder and liquid feeders, the twin screw wet granulator-chopper, the conveying, loading, and leveling means, the drying apparatus, the conveying means, and the mill is controlled to adjust the uniformity of distribution.

9. The system of Claim 1 wherein the twin screw wet granulator-chopper comprises two or more screws having interengaging threads adapted to rotate in the same or opposite directions and granulate the active ingredient and additives.

10. The system of Claim 1 further comprising after Step (b), the step of milling the wet granulation into particles of a desired size.

11. In a method for making a compressible pharmaceutical granulation by mixing at least one pharmaceutically active ingredient with excipients, binders, and liquids to form a wet mixture, chopping said wet mixture into a wet granulation, and drying said wet granulation, the improvement comprising:

forming said wet granulation in a twin screw wet granulator-chopper by feeding at least one pharmaceutically active ingredient, excipients, binders, and liquids to said granulator-chopper at preselected locations along the length thereof removing said granulation continuously, without extrusion, at one end of said granulator-chopper, and drying said granulation.

12. The method of Claim 11 wherein the screws have progressively reduced pitches.

13. The method of Claim 11 wherein said wet mixture is granulated by the rotation of twin screws of said granulator-chopper, said screws having interengaging threads adapted to rotate in the same or opposite directions and granulate said mixture.

14. The method of Claim 13 wherein said wet mixture is granulated by thread-free zones of said screws and said granulated mixture is chopped to form discrete granulation particles.

15. The method of Claim 14 wherein the thread-free zones comprise at least one member from the group consisting of kneading discs, combing mixers, gear mixers, pin mixers, and calender gap mixers.

16. In a method for making a compressible pharmaceutical granulation by mixing a pharmaceutically active compound with excipients, binders, and liquids to form a wet mixture which is then granulated and dried, the improvement comprising drying said granulation using dielectric energy in a single pass, continuous mode.

17. The method of Claim 16 wherein said granulation is dried using radio frequency (RF), low frequency microwave, or high frequency microwave energy in a drying apparatus, said drying apparatus having a gradient with progressively decreasing moisture content in said granulation as said granulation moves along said drying apparatus.

18. The method of Claim 17 wherein said granulation is dried by an alternating electric field produced by a generator of RF energy.

19. An apparatus for drying a pharmaceutical granulation comprising:

a conveying belt for receiving and transporting the granulation to be dried;

a drying tunnel for receiving the granulation, said tunnel containing a source of dielectric energy and electrodes for producing an alternating electric field to heat the granulation;

a source of heated and cooled air;

a flow control mechanism for controlling the flow of heated and cooled air in the tunnel, the flow control mechanism removing moisture from the tunnel; and

control means for controlling the energy and air flow in the tunnel.

20. The apparatus of Claim 19 wherein the dielectric energy is radio frequency energy.

21. The apparatus of Claim 19 wherein the dielectric energy is low frequency or high frequency microwave energy.

22. The apparatus of Claim 19 wherein the direction of the flow of heated and cooled air in the tunnel is co-current or counter current with the direction of the granulation being transported on the drying belt.

23. A twin screw wet granulator-chopper for granulating an active ingredient and additives comprising:

a housing containing feed points for solids and liquids containing at least one active ingredient and additives;

twin screws within the housing, the screws having interengaging threads adapted to rotate in the same or opposite directions;

a motor for rotating the twin screws to mix the solids and liquids into a granulation;

an open end for discharging the granulation; and

means for chopping the granulation into discrete particles.

24. The twin screw wet granulator-chopper of Claim 23 further comprising one or both of reverse threads and thread-free zones for granulating the solids and liquids.

25. The twin screw wet granulator-chopper of Claim 23 further comprising at least one member from the group consisting of kneading discs, combing mixers, gear mixers, pin mixers, and calender gap mixers, for granulating the solids and liquids.

26. The twin screw wet granulator-chopper of Claim 23 wherein the chopping means is flush with the open end or extends beyond the open end of the twin screw wet granulator-chopper.

27. A continuous processing system for producing a high dose pharmaceutical granulation comprising:

a twin screw wet granulator-chopper;

a powder feeder adapted to feed a powder to said twin screw wet granulator-chopper, said powder comprising a pharmaceutically active ingredient;

a first liquid feeder adapted to feed a liquid to said twin screw wet granulator-chopper;

wherein said powder feeder and said liquid feeder are coupled to said twin screw wet granulator-chopper and adapted to feed said powder and said liquid at an inlet of said twin screw wet granulator-chopper; and,

wherein said powder and said liquid flow through said twin screw wet granulator-chopper from said inlet to an outlet of said twin screw wet granulator-chopper;

said twin screw wet granulator-chopper comprising:

a) a first conveying element having at least one conveying element pitch;

b) a second conveying element having at least one conveying element pitch and positioned to contact said pharmaceutically active ingredient after said first conveying element, wherein said second conveying element has at least one pitch less than at least one pitch of said first conveying element;

c) a first mixing element positioned in between said first and said second conveying elements;

d) at least one chopping element positioned to contact said pharmaceutically active ingredient after said second conveying element; and

a housing surrounding said elements, said housing defining said inlet, and a nonextruding opening at said outlet.

28. The continuous processing system of Claim 27 further comprising:

a third conveying element having at least one conveying element pitch, said third conveying element positioned to contact said pharmaceutically active ingredient after said second conveying element and before said chopping element, wherein at least one pitch of said third conveying element is less than at least one pitch of said second conveying element; and

a second mixing element positioned in between said second and said third conveying elements.

29. The continuous processing system of Claim 27, further comprising a second liquid feeder.

30. The continuous processing system of Claim 27, wherein said powder feeder and said first liquid feeder are both coupled to said twin screw wet granulator-chopper at a position where said first conveying element is positioned in said housing.

31. The continuous processing system of Claim 30, wherein said second liquid feeder is coupled to said twin screw wet granulator-chopper at a position between where said first conveying element and said first mixing element are positioned in said housing.

32. The continuous processing system of Claim 27, wherein said active pharmaceutical ingredient comprises nelfinavir mesylate.

33. The continuous processing system of Claim 33, wherein said powder further comprises calcium silicate.

34. The continuous processing system of Claim 34, wherein the ratio of nelfinavir mesylate to calcium silicate is between 3:1 and 5:1.

35. The continuous processing system of Claim 34, wherein the ratio of nelfinavir mesylate to calcium silicate is 4:1.

36. The continuous processing system of Claim 27, wherein said liquid comprises water.

37. The continuous processing system of Claim 27, wherein said first mixing element is positioned immediately adjacent both of said first conveying element and said second conveying element.

38. A method for producing a high dose pharmaceutical granulation comprising:

(a) feeding a powder comprising a pharmaceutically active ingredient to a twin screw wet granulator-chopper, said powder having a

(b) feeding a liquid to said twin screw wet granulator-chopper;

(c) contacting said liquid and said powder with a first conveying element of said twin screw wet granulator-chopper, said first conveying element having at least one pitch;

(d) contacting said liquid and said powder with a first mixing element of said twin screw wet granulator-chopper to form a wet mass;

(e) contacting said wet mass with a second conveying element of said twin screw wet granulator-chopper, said second conveying element having at least one pitch, wherein at least one pitch of said second conveying element is less than at least one pitch of said first conveying element; and

(f) contacting said wet mass with a chopping element of said twin screw wet granulator-chopper and chopping said wet mass into a granulation.

39. The method of Claim 42, further comprising the steps of:

(a) contacting said wet mass with a third conveying element of said twin screw wet granulator-chopper, said third conveying element having at least one pitch, wherein at least one pitch of said third conveying element is less than at least one pitch of said second conveying element; and

(b) contacting said wet granulation with a second mixing element; wherein the steps of contacting said wet mass with said third conveying element and contacting said wet granulation with said second mixing element are performed after the step of contacting said wet mass with said second conveying element and before the step of contacting said wet mass with said chopping element.

40. The method of Claim 42, wherein the temperature of said twin screw wet granulator-chopper is maintained at a temperature between 15°C and 90°C.

41. A pharmaceutical formulation comprising the pharmaceutical granulation produced according to the method of Claim 11.

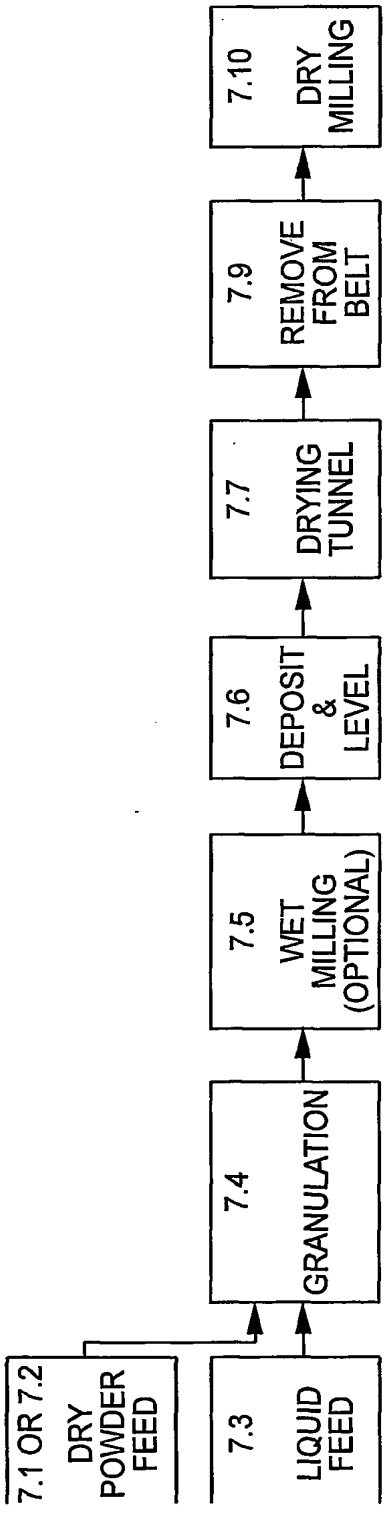
7.1 OR 7.2
DRY POWDER FEED
7.3
LIQUID FEED
7.4
GRANULATION
7.5
WET MILLING (OPTIONAL)
7.6
DEPOSIT & LEVEL
7.7
DRYING TUNNEL
7.9
REMOVE FROM BELT
7.10
DRY MILLING

FIG. 1

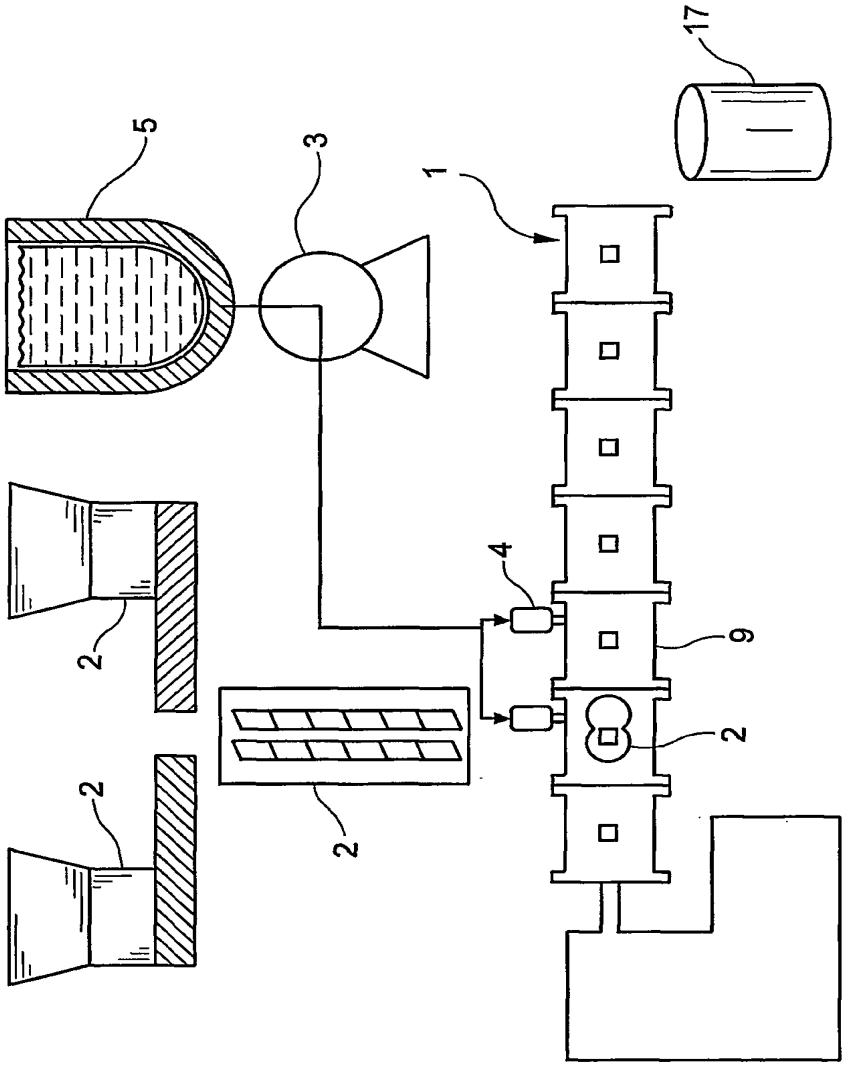

FIG. 2

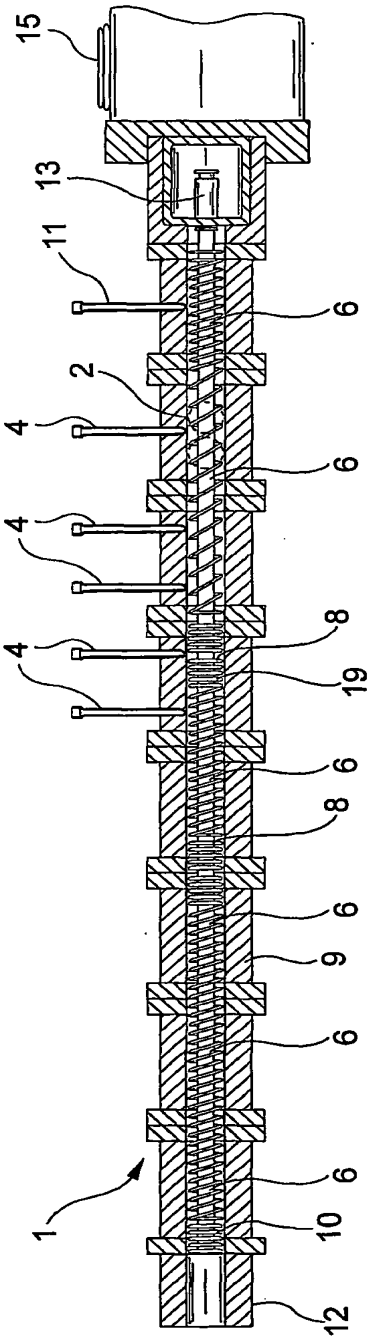

FIG. 3A

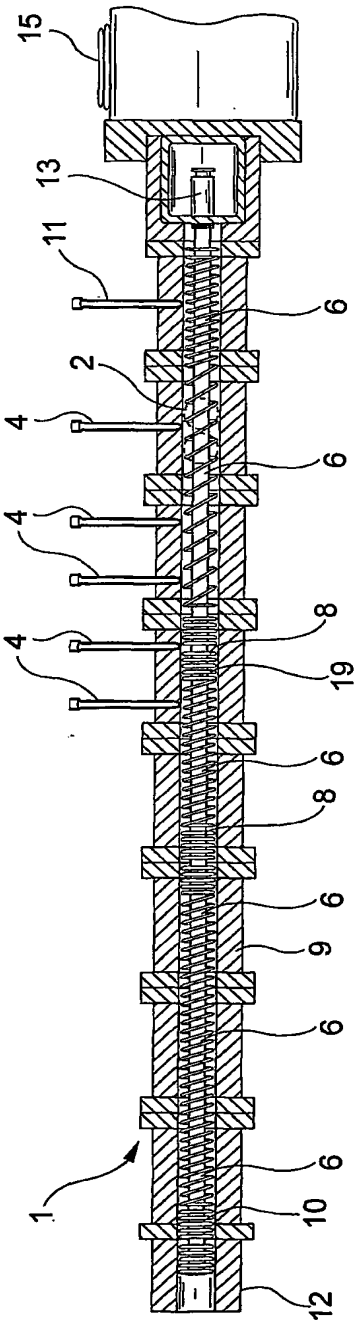

FIG. 3B

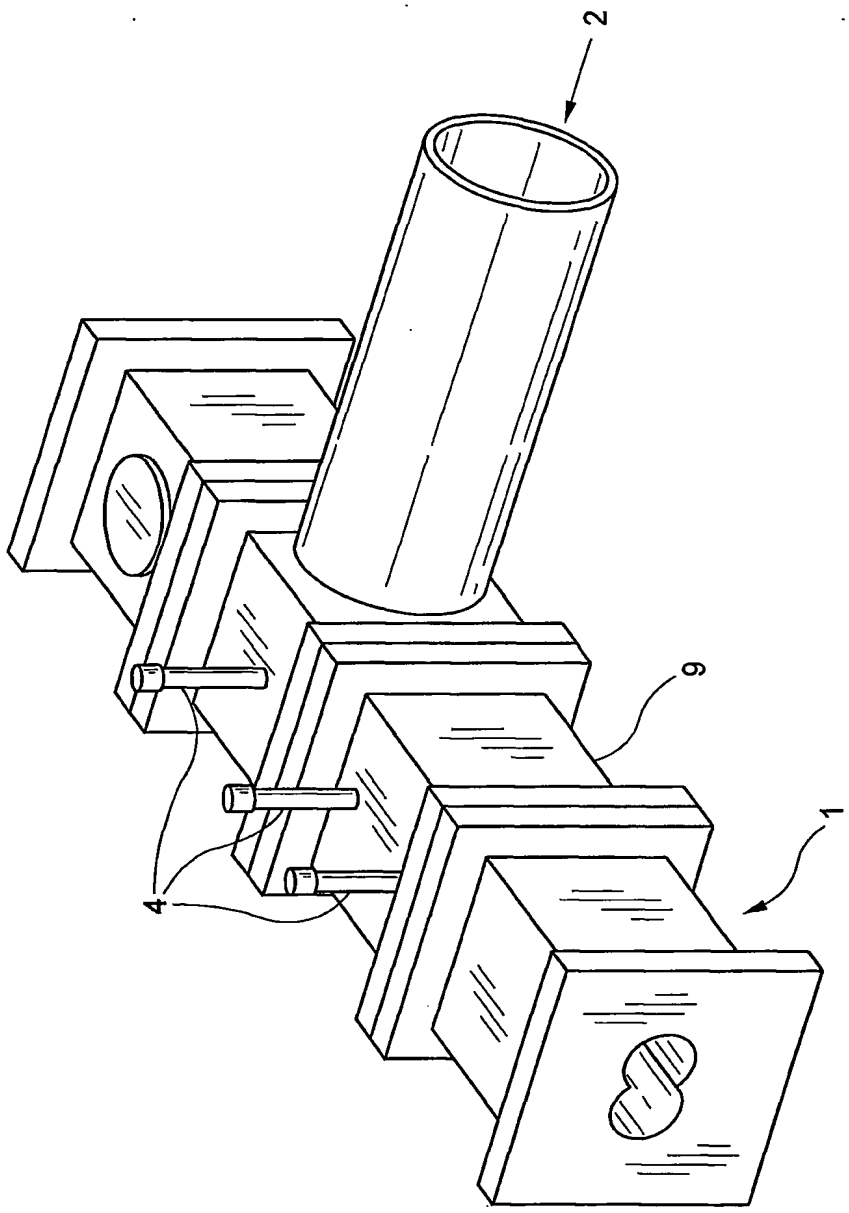

FIG. 4

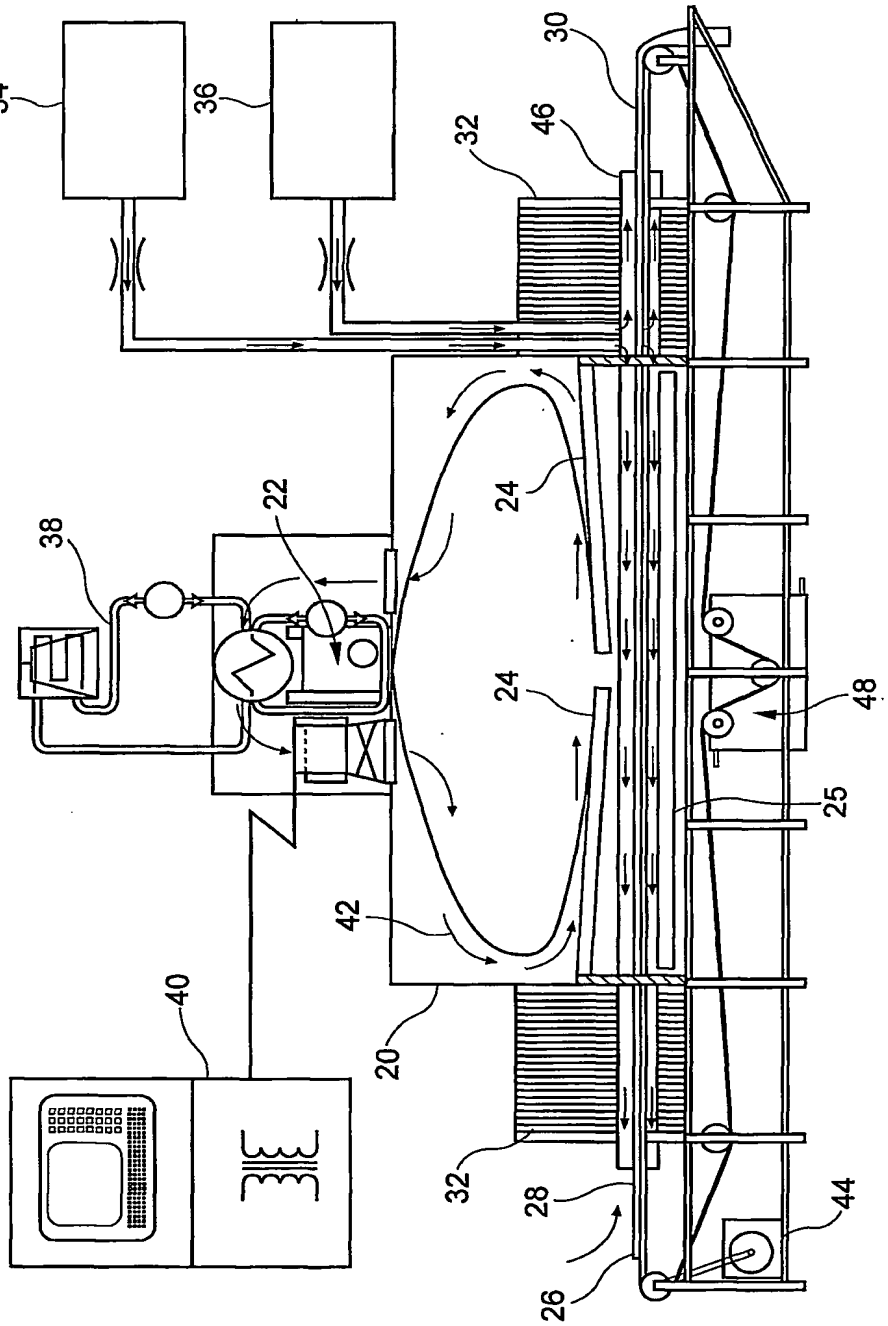

FIG. 5

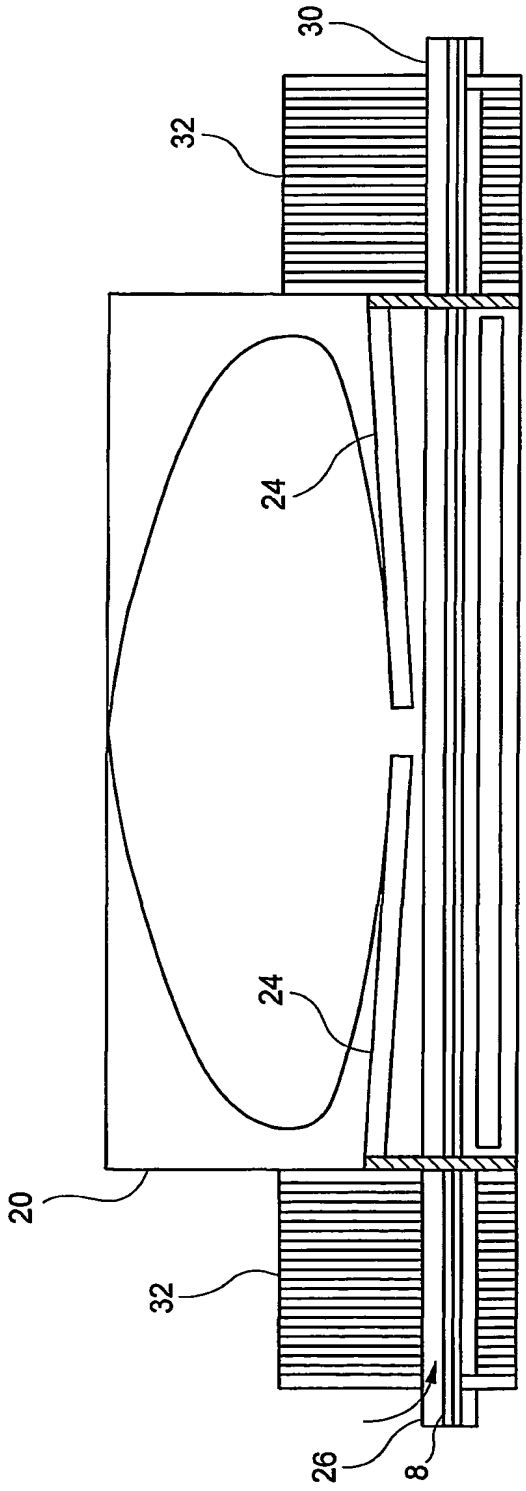

FIG. 6